



# **Introducing LATE: An important underpinning of dementia in later life**

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# Disclosure

**S. Ahmad Sajjadi consults for Guide point Global.**

**He has also served on advisory board for Eisai.**



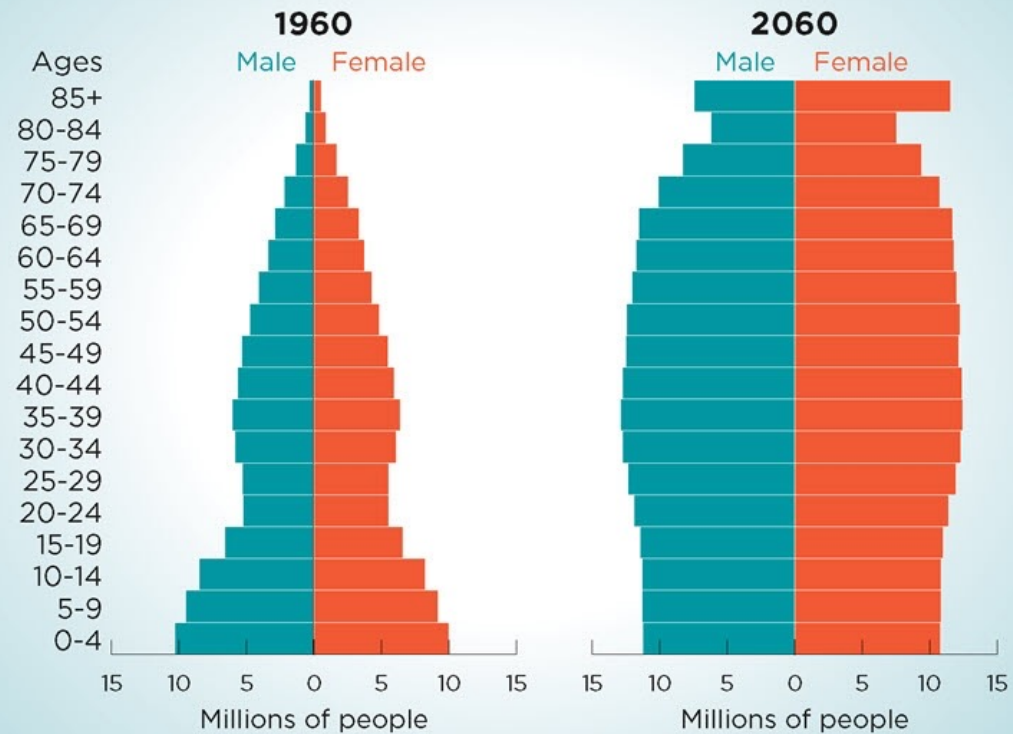


# Outline

- **Introduction and historical background**
  - **Introducing Limbic predominant age related TDP-43 encephalopathy (LATE)**
  - **Cognitive impact of LATE**
- 
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# From Pyramid to Pillar: A Century of Change

Population of the United States



United States™  
**Census**  
Bureau

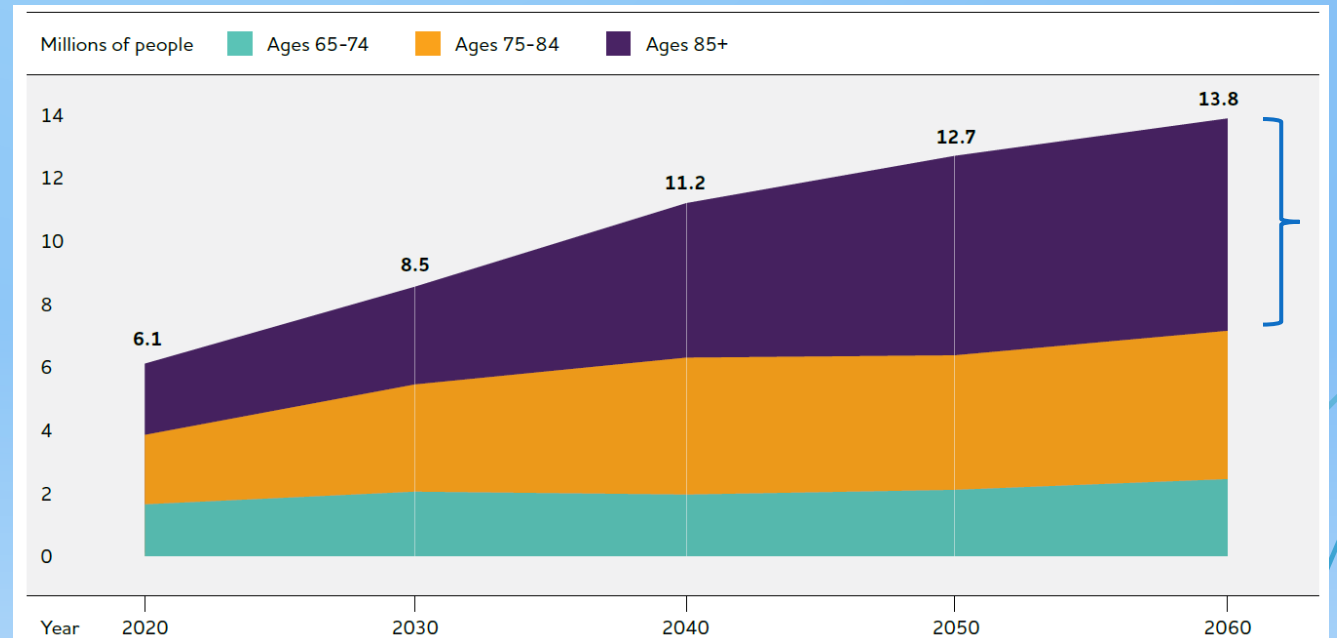
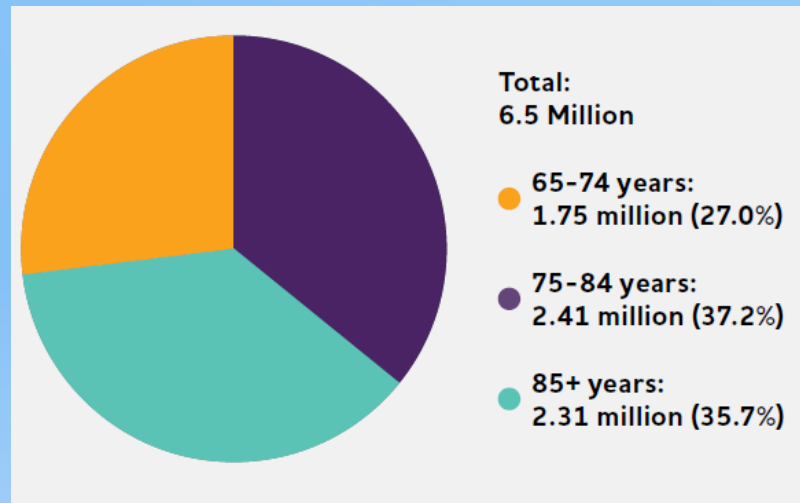
U.S. Department of Commerce  
Economics and Statistics Administration  
U.S. CENSUS BUREAU  
[census.gov](https://www.census.gov)

Source: National Population  
Projections, 2017  
[www.census.gov/programs-surveys/popproj.html](https://www.census.gov/programs-surveys/popproj.html)

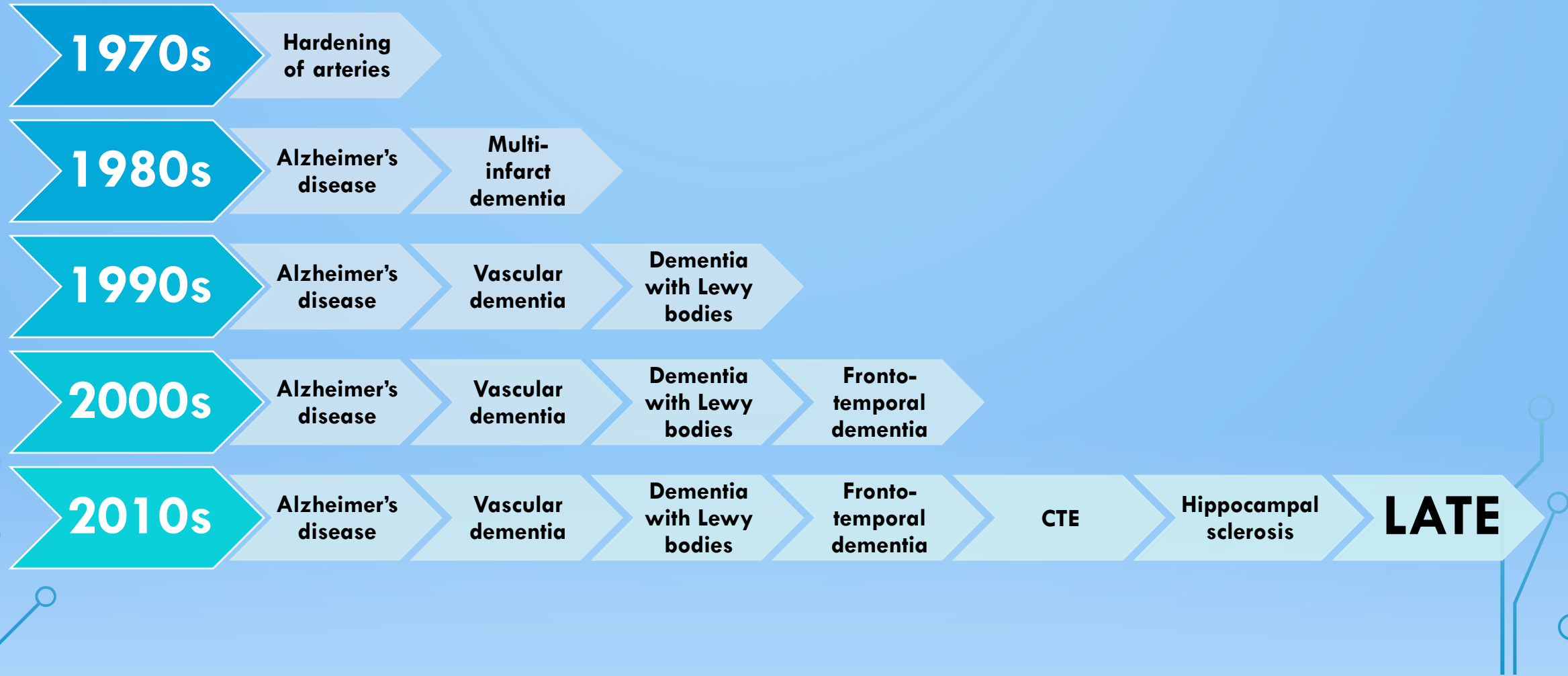


# Projections for Alzheimer's disease

- Alzheimer's disease and related dementia (ADRD) are the health care tsunamis of the 21<sup>st</sup> century
- The oldest old are the fastest growing segment with highest rates of dementia

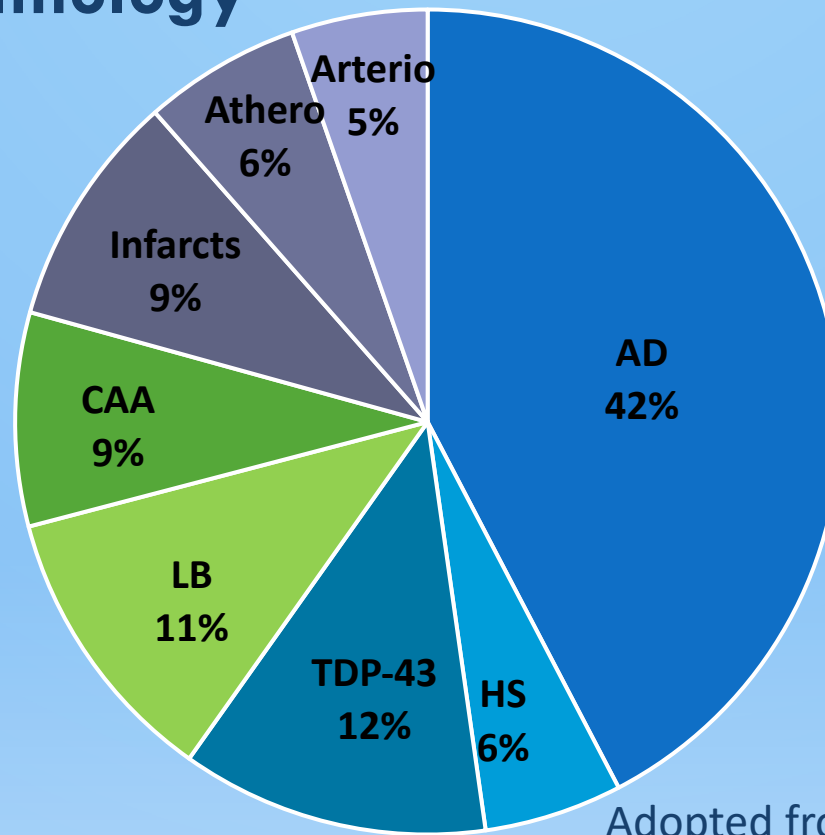


# Evolution of dementia nosology



# Etiology of Alzheimer's dementia

- Disconnect between Alzheimer's clinical syndrome and Alzheimer's pathology



Adopted from PA Boyle, et al. Ann Neurol 2019; 85:114-124

The background is a solid light blue. On the left side, there are several vertical lines of varying heights, some ending in small circles, resembling a circuit board or a data stream. On the right side, there are a few more vertical lines, also ending in small circles, and some horizontal lines connecting them.

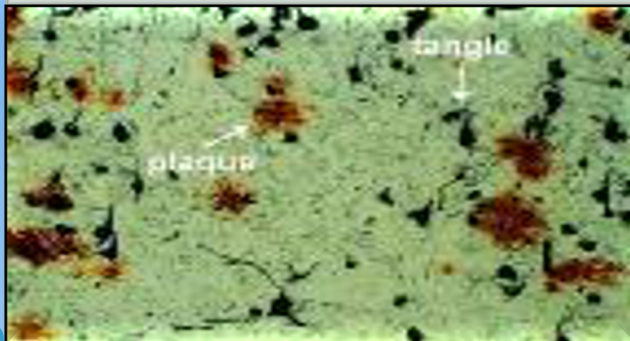
**TDP-43**

# TDP-43

- **TransActive Response (TAR) DNA binding protein of 43 kDa**
- **Ubiquitously present in all cell nuclei**
- **Regulator of gene expression**
- **Bad when it gets trapped in cytoplasm**

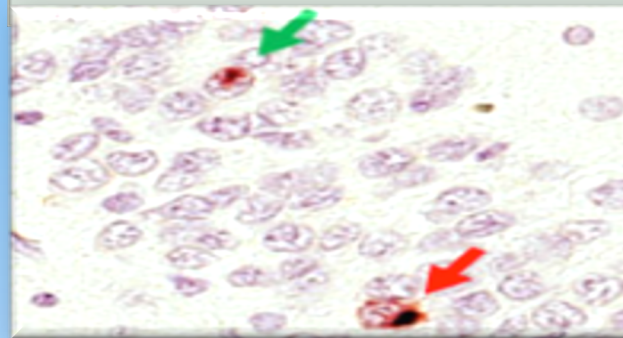
## Frontotemporal dementia

- Primary tauopathy
- **TDP-43**



## Alzheimer's dementia

- Amyloid  $\beta$  plaques
- Tau tangle
- **TDP-43**



## Hippocampal sclerosis

- **TDP-43**
- Arteriolo-sclerosis



# TDP-43 and dementia syndromes

**Frontotemporal  
dementia**

**Alzheimer's disease**

**Hippocampal sclerosis**

***50-60 years***

***70-80 years***

***> 85 years***

# LATE

doi:10.1093/brain/awz099



BRAIN 2019; 142; 1503–1527 | 1503

## BRAIN

A JOURNAL OF NEUROLOGY

### REVIEW

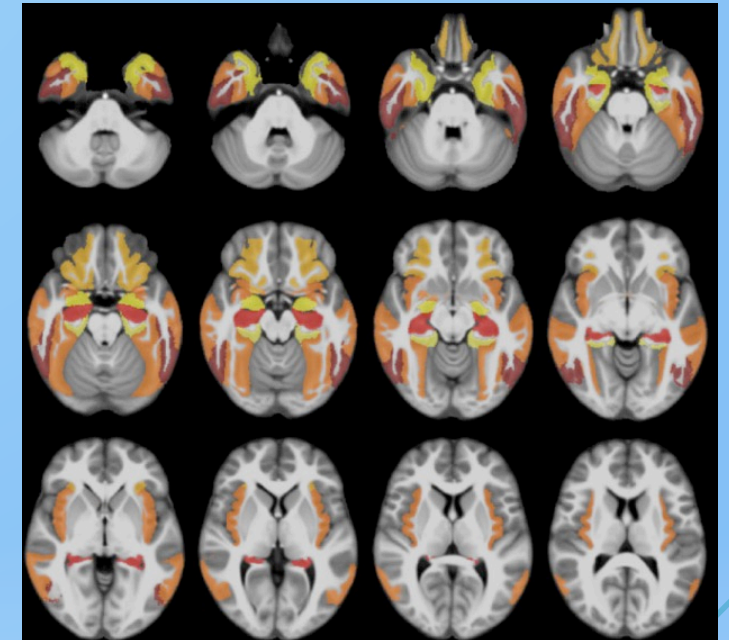
## Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,<sup>1</sup>  Dennis W. Dickson,<sup>2</sup> John Q. Trojanowski,<sup>3</sup> Clifford R. Jack Jr.,<sup>4</sup> Patricia A. Boyle,<sup>5</sup> Konstantinos Arfanakis,<sup>5,6</sup> Rosa Rademakers,<sup>2</sup> Irina Alafuzoff,<sup>7</sup> Johannes Attems,<sup>8</sup> Carol Brayne,<sup>9</sup> Ian T.S. Coyle-Gilchrist,<sup>9</sup> Helena C. Chui,<sup>10</sup> David W. Fardo,<sup>1</sup> Margaret E. Flanagan,<sup>11</sup> Glenda Halliday,<sup>12</sup> Suvi R.K. Hokkanen,<sup>9</sup> Sally Hunter,<sup>9</sup> Gregory A. Jicha,<sup>1</sup> Yuriko Katsumata,<sup>1</sup> Claudia H. Kawas,<sup>13</sup> C. Dirk Keene,<sup>14</sup> Gabor G. Kovacs,<sup>15</sup> Walter A. Kukull,<sup>14</sup> Allan I. Levey,<sup>16</sup> Nazanin Makkinejad,<sup>6</sup> Thomas J. Montine,<sup>17</sup> Shigeo Murayama,<sup>18</sup> Melissa E. Murray,<sup>2</sup> Sukriti Nag,<sup>5</sup> Robert A. Rissman,<sup>19</sup>  William W. Seeley,<sup>20</sup> Reisa A. Sperling,<sup>21</sup> Charles L. White III,<sup>22</sup> Lei Yu<sup>5</sup> and Julie A. Schneider<sup>5</sup>



# LATE-NC

- **TDP-43 pathology in limbic structures in those  $> 85$  y/o**
  - Present in  $> 30\%$  of autopsied brains
  - Associated with an amnestic syndrome
  - Clinically diagnosed as Alzheimer's during life
- **4 stages:**
  - Stage 0: no TDP-43 pathology
  - Stage 1: confined to amygdala
  - Stage 2: spread to hippocampus
  - Stage 3: involvement of middle frontal gyrus



Nelson et al. Brain, 2019

Nelson et al. Acta Neuropathological 2022

# The 90+ Study

- **Community based cohort in Southern California**
- **Longitudinal assessments**
- **High autopsy rates**
- **Available biomarkers**

# NACC

- **National database of Alzheimer's disease research centers (ADRC)**
- **Longitudinal assessments**
- **High number of participants**
- **Uniform pathology dataset**

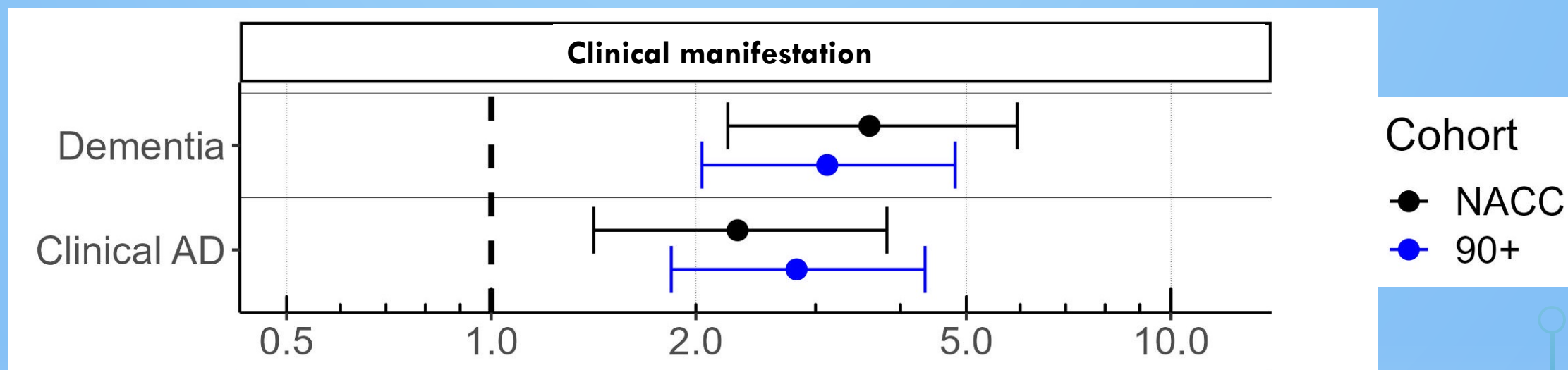
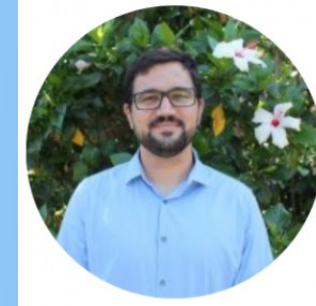
# Demographics

	The 90+ Study	
	LATE-NC (N=149, 36%)	Other (N=258, 64%)
Age at Death (Mean (SD))	98 ( $\pm$ 3.7)	97 ( $\pm$ 3.5)
Female	104 (69.8%)	178 (69.0%)
College or More education	79 (53.0%)	127 (49.2%)
Dementia	90 (60.4%)	88 (34.1%)

# Demographics

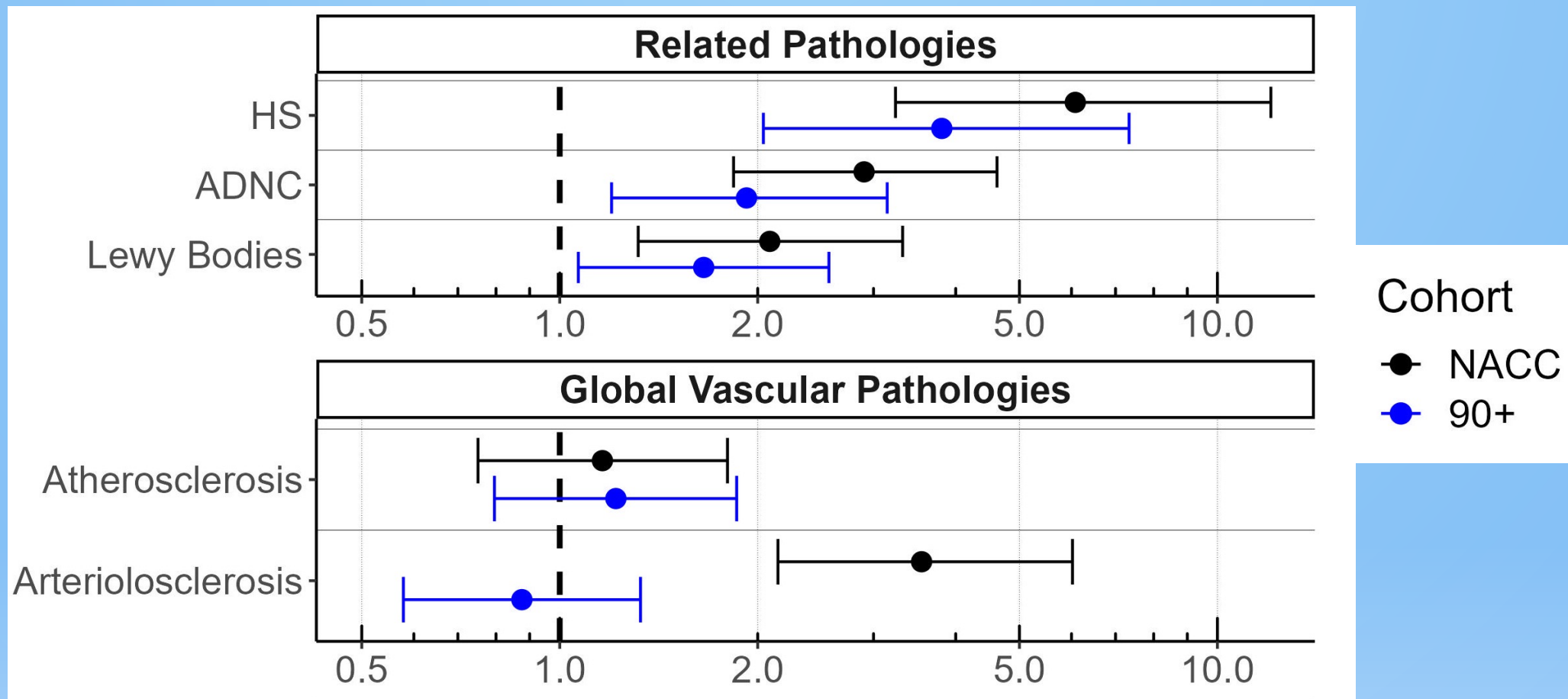
	The 90+ Study		NACC (>90 years old)	
	LATE-NC (N=149, 36%)	Other (N=258, 64%)	LATE-NC (N=144, 41%)	Other (N=203, 59%)
Age at Death (Mean (SD))	98 ( $\pm$ 3.7)	97 ( $\pm$ 3.5)	94 ( $\pm$ 3.7)	94 ( $\pm$ 3.5)
Female	104 (69.8%)	178 (69.0%)	83 (57.6%)	116 (57.1%)
College or More education	79 (53.0%)	127 (49.2%)		
Dementia	90 (60.4%)	88 (34.1%)	113 (78.5%)	103 (50.7%)

# Is LATE related to dementia and clinical Alzheimer's?

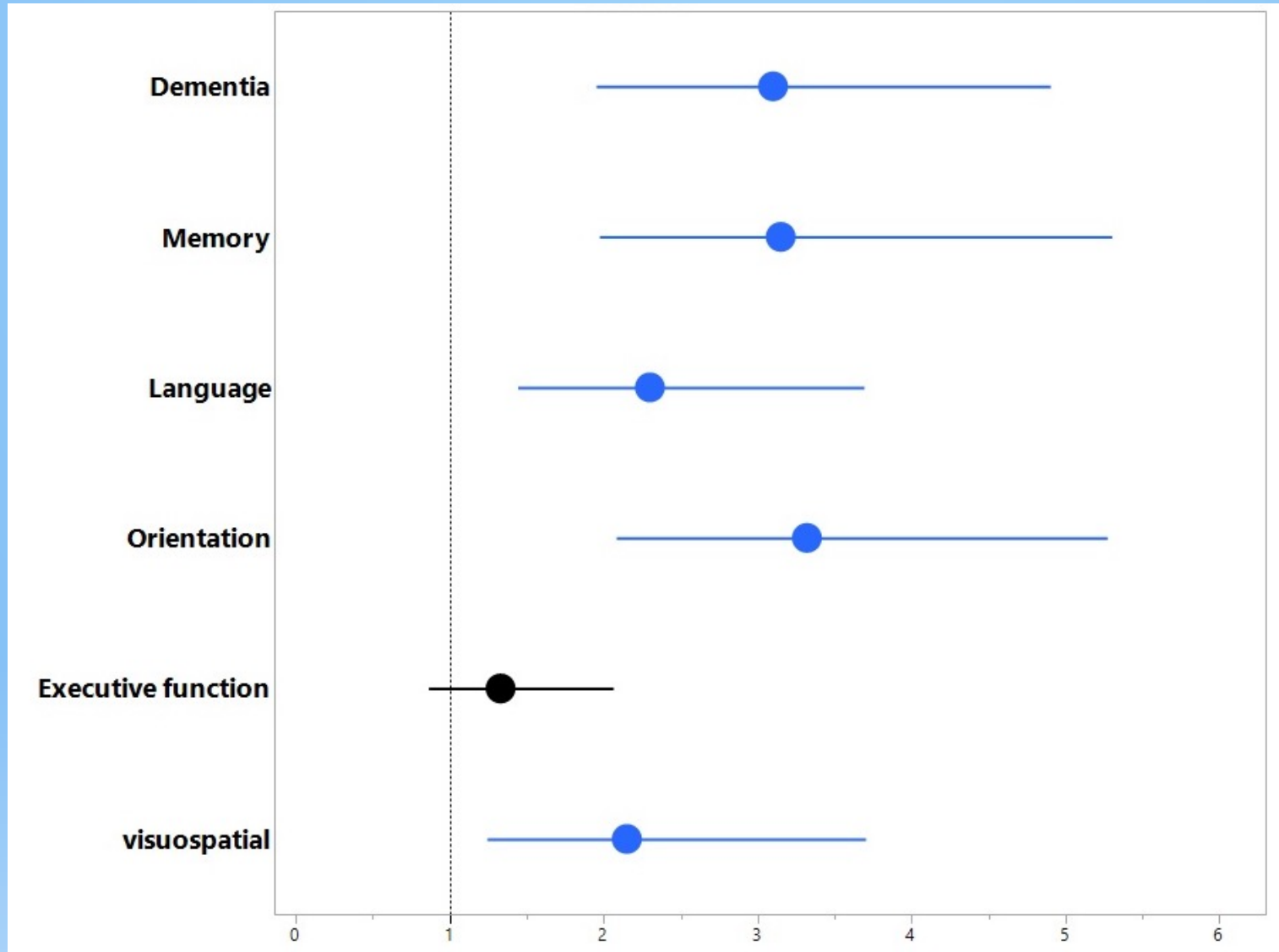


Unpublished

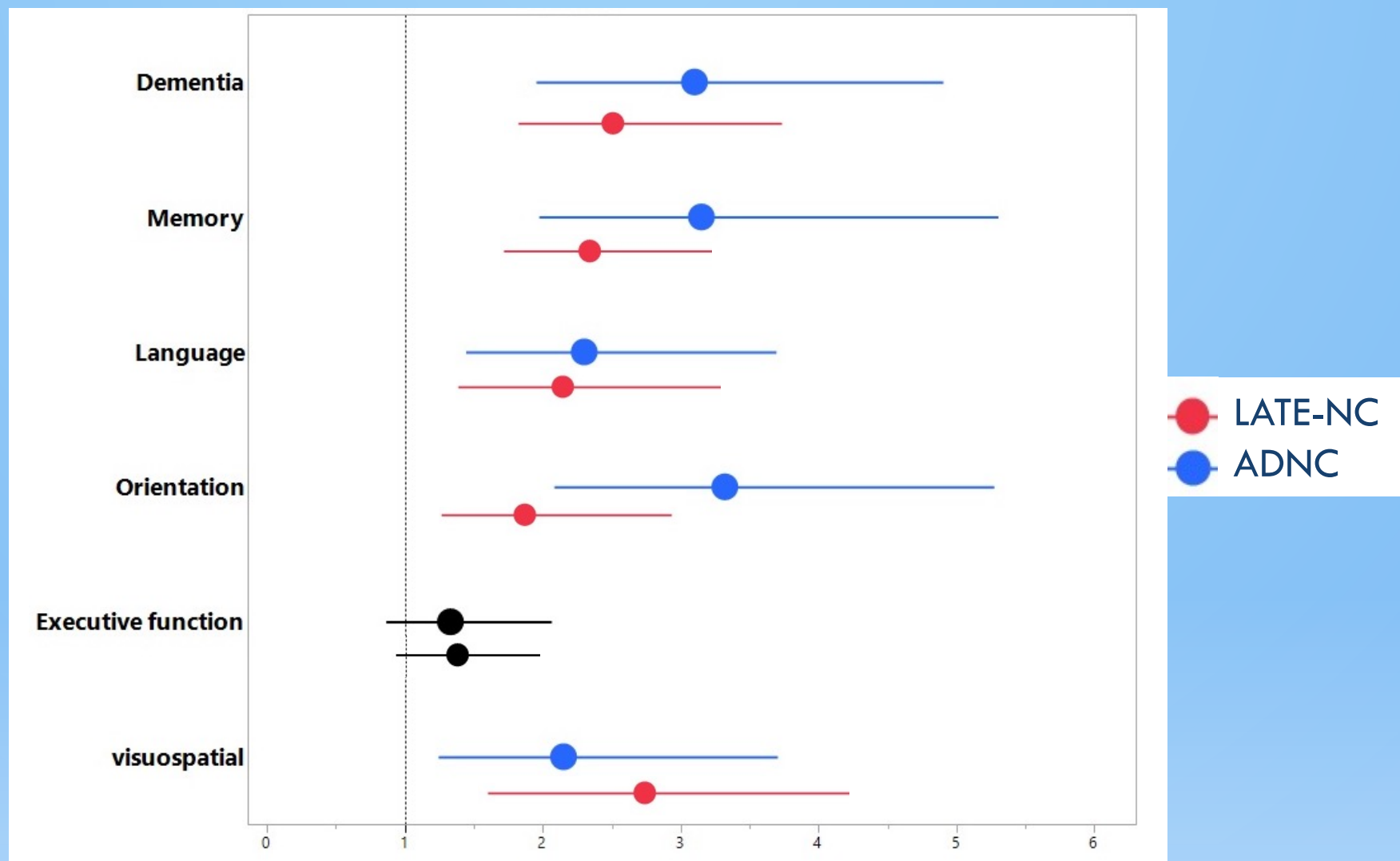
# How is LATE related to other pathologies?



# Relationship with cognitive domains (The 90+ Study)



# Comparison with Alzheimer's pathology

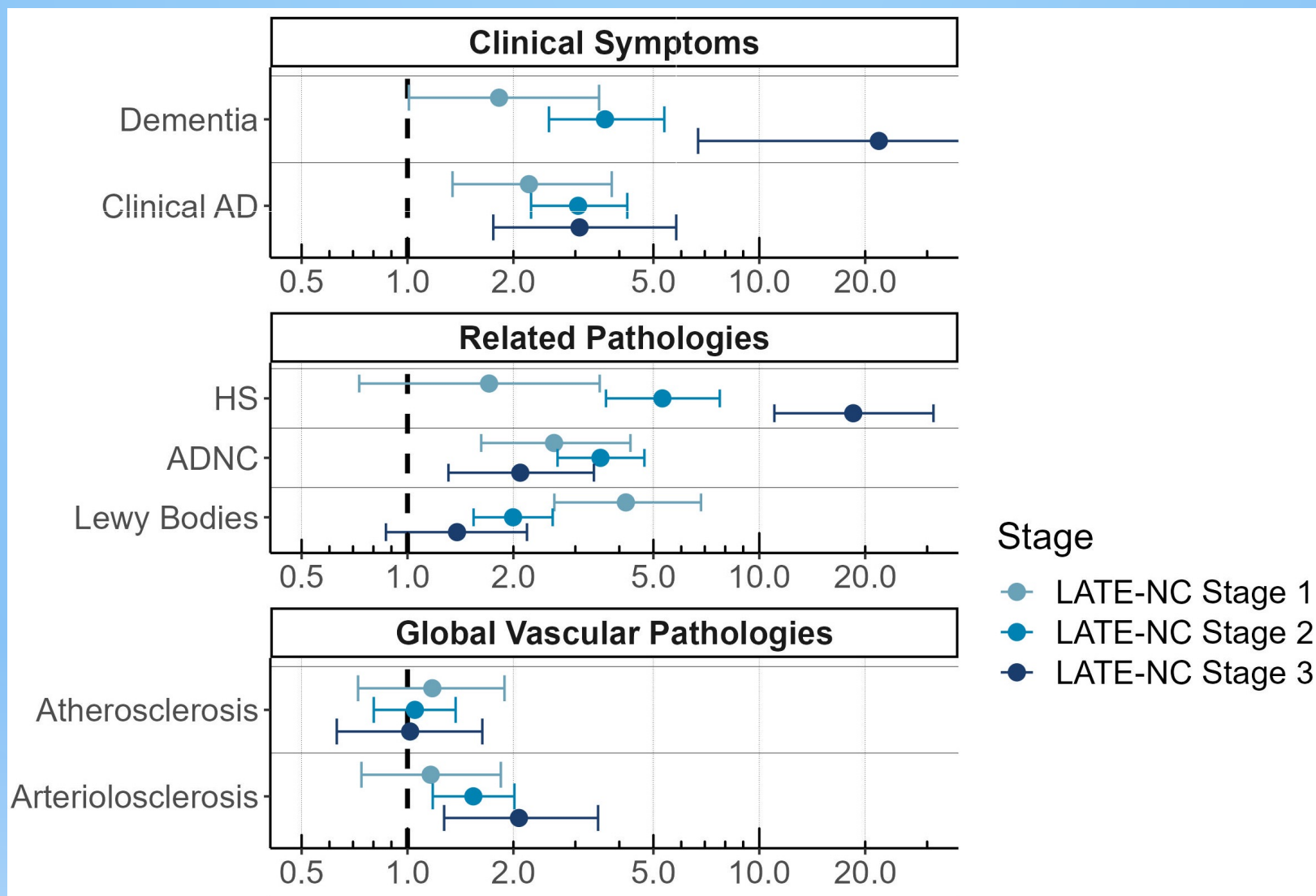




# LATE-NC in the full NACC cohort

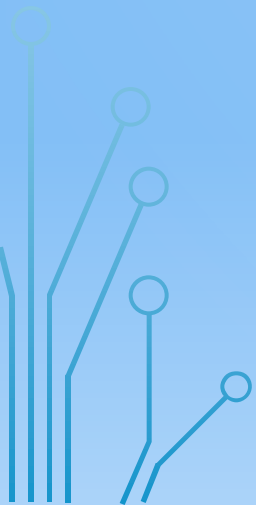
	LATE-NC (N=508, 32%)	Other (N=1083, 68%)
Age at Death (Mean (SD))	84 ( $\pm$ 9.5)	78 ( $\pm$ 12)
Female	259 (51.0%)	490 (45.2%)
Education years (Mean (SD))	16 ( $\pm$ 3.0)	16 ( $\pm$ 3.0)
Dementia	451 (88.8%)	820 (75.7%)

# Associations by stages of LATE-NC (NACC)





# Conclusion

- **LATE-NC is a common degenerative pathology**
  - **LATE-NC is related to dementia and impairment in cognitive domains**
  - **Its cognitive signature is very similar to Alzheimer's disease pathology**
  - **It remains a postmortem diagnosis**
- 

# Acknowledgement

- ***The 90+ Study***

Claudia Kawas

Maria Corrada

Natalie Bryant



- ***Sajjadi Lab***

Davis Woodworth

Katelynn Nguyen

Anne-Marie Leiby

Hannah Nguyen

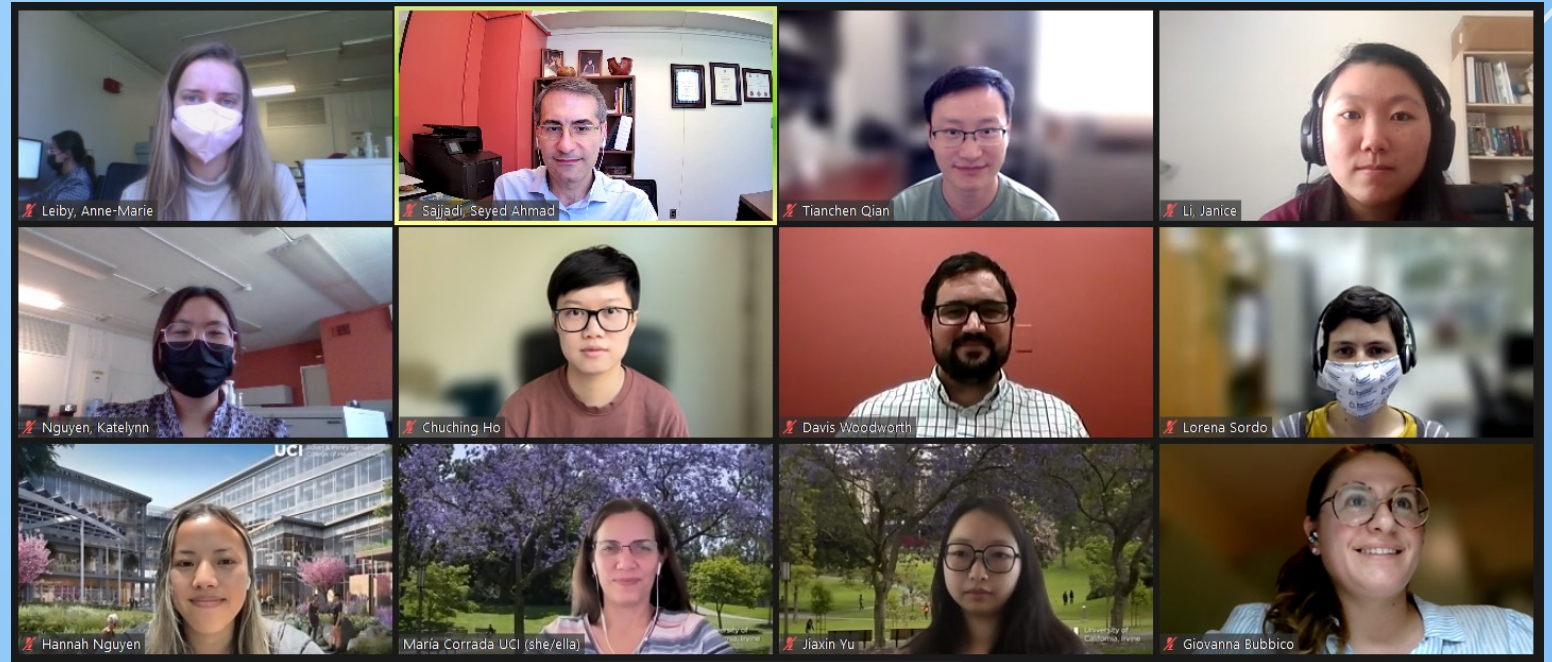
Kiana Scambray



- ***Stanford Team***

Thomas Montine

Syed Bukhari



**R01AG21055; PI: Kawas, Corrada**

**R01AG062706; PI: Sajjadi**

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# Thank you

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# LATE stages results

